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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,631	07/28/2003	Marc Achen	029065.48666C1	3314

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,631	ACHEN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-27 and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-27 and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/28/03* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 8-27 and 36-44 are pending and are being acted upon in this Office Action.

2. Claims 9-13, 15-17, 19-22, 24-27, 37-39 and 41-44 are objected to because "A" should have been "The" for said dependent claims.

3. Claim 14 is objected to because "or" is missing in the phrase "VEGF-D in or on blood vessel endothelial cell **or** in or around a potential neoplastic growth is indicative of a neoplastic disease."

4. The drawing, filed 7/28/03, is not approved. Specifically, Figure 18 is too dark. Appropriate action is required.

5. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/956,095, filed 9/20/01, which is now abandon and 09/796,714, filed 3/2/01, which is now abandon.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-27 and 36-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for screening for a neoplastic disease such as malignant melanoma, breast ductal carcinoma, squamous cell carcinoma, prostate cancer and endometrial cancer characterized by an increase in expression of VEGF-D using labeled monoclonal antibody such as 4A5, 5F12 and 2F8 that specifically binds to human VEGF-D, **does not** reasonably provide enablement for (1) a method for screening for any neoplastic disease characterized by an increase in expression of VEGF-D, comprising obtaining a sample from an organism suspected of being in a neoplastic disease state characterized by an increase in expression of VEGF-D, exposing said sample to *any* composition comprising *any* "compound", that specifically binds any VEGF-D, *any* monoclonal antibody which specifically binds any

VEGF-D, *any* antibody that binds to the VEGF "homology domain" of VEGF, or *any* "compound" includes a detectable label; washing said sample, and screening for said disease by detecting the presence, quantity or distribution of said "compound" in said sample, where detection of VEGF-D in or on blood vessel endothelial cells in or around a potential neoplastic growth is indicative of a neoplastic disease (2) a method for screening for tumor for metastatic risk, said method comprising exposing a tumor sample to any composition comprising any "compound" that specifically binds VEGF-D, *any* monoclonal antibody that specifically binds VEGF-D, *any* monoclonal antibody that binds to the VEGF homology domain of VEGF-D, *any* "compound includes a label"; washing said sample and screening for metastatic risk by detecting the presence, quantity or distribution of said "compound" in sample, where expression of VEGF-D by said tumor is indicative of metastatic risk, and (3) a method of detecting micro-metastasis of any neoplastic disease state characterized by an increase in expression of VEGF-D comprising exposing a tissue sample to any composition comprising *any* "compound" that binds VEGF-D, *any* monoclonal antibody which specifically binds VEGF-D, *any* antibody binds to VEGF "homology domain" of VEGF-D, and *any* "compound includes a detectable label". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three monoclonal antibodies 4A5, 5F12 and 2F8 (renamed VD1, VD2 and VD3, respectively) that bind specifically to the VEGF homology domain of VEGF-D of SEQ ID NO: 3, commercially available monoclonal antibody against human VEGFR-2 and polyclonal antibodies against VEGFR-3 for immunohistochemical analysis of invasive malignant melanomas (page 48).

The specification does not teach how to make *any* "compound" or *any* "compound includes a label" because the term "compound" has no structure, much less using the undisclosed

"compound" for a method of for screening for any neoplastic disease characterized by an increase in expression of VEGF-D, a method for screening for tumor for metastatic risk or for a method of detecting micro-metastasis of any neoplastic disease state characterized by an increase in expression of VEGF-D.

Stryer *et al*, PTO 1449, teach that the primary amino acid sequence determines the conformational structure of the protein (See enclosed relevant pages).

Without the specific amino acid sequence or the chemical structure, it is unpredictable which undisclosed "compound" or "compound includes a label" would bind specifically to VEGF-D, let alone making the undisclosed "compound" for a method of screening for any neoplastic disease characterized by an increase in expression of VEGF-D. Further, there is inadequate working example demonstrating the binding specificity of any undisclosed "compound" to VEGF-D, VEGFR-2 and/or VEGFR-3, in turn, for a method for screening any neoplastic disease characterized by an increase in expression of VEGF-D. Given the indefinite number of undisclosed "compound", it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

With regard to monoclonal antibody that binds to any "VEGF-D" or *any* monoclonal antibody that binds to "homology region" of VEGF-D, there is insufficient guidance as to the "homology domain" without the amino acid residues in reference to a sequence of which VEGF-D. Further, there is insufficient guidance as to the binding specificity of any monoclonal antibody that binds to the "VEGF homology domain of VEGF-D" because all members of the VEGF family have the same "homology domain".

Kuby *et al*, PTO 1449, teach that immunizing a peptide such as a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Abaza *et al*, PTO 1449, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Further, there is sufficient working example demonstrating any monoclonal that binds to VEGF-D or any monoclonal antibody that binds to the homology domain of VEGF-D does not cross-react with other members of the VEGF family since all members of the VEGF family have the same "homology domain". Given the unlimited number of undisclosed "monoclonal antibody

that binds to VEGF-D" and the lack of binding specificity for monoclonal antibody that binds to the "homology domain of VEGF-D", it is unpredictable which antibody will bind specifically to which VEGF-D or the homology domain of VEGF-D, in turn, would be useful for a method for screening for tumor for metastatic risk. Since the compound is not enabled, it follows that the compound includes a detectable label is not enabled. Claim 41 is included in this rejection because the claimed method depends from the undisclosed compound in claim 40.

For the above reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 8-27 and 36-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* "compound" that specifically binds VEGF-D for a method for screening a neoplastic disease characterized by an increase expression of VEGF-D or for a method of screening a tumor for metastatic risk or a method of detecting micro-metastasis of a neoplastic disease state characterized by an increase in expression of VEGF-D, (2) *any* compound is *any* monoclonal antibody which specifically binds any VEGF-D for a method for screening a neoplastic disease characterized by an increase expression of VEGF-D or for a method of screening a tumor for metastatic risk or a method of detecting micro-metastasis of a neoplastic disease state characterized by an increase in expression of VEGF-D.

The specification discloses only three monoclonal antibodies 4A5, 5F12 and 2F8 (renamed VD1, VD2 and VD3, respectively) that bind specifically to the VEGF homology domain of VEGF-D of SEQ ID NO: 3, commercially available monoclonal antibody against

human VEGFR-2 and polyclonal antibodies against VEGFR-3 for immunohistochemical analysis of invasive malignant melanomas (page 48).

With the exception of the specific monoclonal antibody mentioned above that binds specifically to SEQ ID NO: 3, there is insufficient written description about the structure associated with function of *any* "compound" without the amino acid sequence. Further, there is inadequate written description about *any* compound is *any* antibody that binds to any VEGF-D or the "homology domain" of VEGF-D because the amino acid residues for "homology domain" in reference to which amino acid sequence of which VEGF-D is required.

Since the compound is not adequately described, it follows that the compound includes a detectable label is not adequately described. Claim 41 is included in this rejection because the claimed method depends from the undisclosed compound in claim 40.

Given the lack of a written description of *any* additional representative species of "compound", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 8-21 and 36-44 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/33485 (July 8, 1999, PTO 1449).

The WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk wherein the reference method steps comprise: (1) obtaining a sample such as a biopsy specimen from patient with melanoma (See page 20, lines 1-10, page 32 at line 18, in particular), (2) exposing the biopsy specimen to a composition comprising a compound such as monoclonal antibody Mab 2F8, 5F12, 4A5 and 4E10 that bind specifically to VEGF-D for immunohistochemistry analysis (See page 32, lines 18-19, in particular), (3) washing the sample (see page 33, line 19, in

particular) and (4) assessing for the presence or increase in the VEGF-D expression in or around a potential neoplastic growth (See pages 33-35, Figs 7A-E, in particular). The reference teaches VEGF-D monoclonal antibodies detected VEGF-D in melanoma cells in both clinical samples, and the detection of VEGF-D indicates these tumor cells are most likely producing said VEGF-D (See page 35, lines 13-15, in particular). The reference VEGF-D antibody binds to VEGF homology domain of VEGF-D such as VEGF-D having a deletion at the N and C terminals (VEGF-DΔNΔC) (See page 29, 15-23; page 31, line 3, Fig 1 in particular) and the reference antibody includes a detectable label such as FITC (See page 20, lines 11-20, claims 28-30 of WO 99/33485 publication, in particular). The WO 99/33485 publication teaches that VEGF-D is detected on the endothelial cells of blood vessels in the vicinity of tumor cells but not detected on more distant vessels (non tumor vessels) (See page 35, lines 14-17, in particular). The recitation of micro-metastasis in claim 40 is within the teachings of WO 99/33485 publication because the WO 99/33485 publication teaches a method for screening for a neoplastic disease such as human malignant melanoma as an indicator of future metastatic risk. Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 8, 12 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/33485 (July 8, 1999, PTO 1449) in view of Achen *et al* (Proc. Nat. Acad. Sci USA 95: 548-553, January 1998; PTO 1449) and Valtola *et al* (American J of Pathology 154(5): 1381-1390, May 1999; PTO 1449) or Salven *et al* (Am J Pathol 153(1): 103-8, July 1998; PTO 1449) or Tsurusaki *et al* (Br J Cancer 80(1-2): 309-13, April 1999; PTO 1449).

The teachings of the WO 99/33485 publication have been discussed supra. The WO 99/33485 publication teaches VEGF-D binds to both VEGFR-2 and VEGFR-3 (see page 45, pages 13-14, in particular) and antibody to VEGFR-2 and VEGFR-3 may also be used since VEGF-D, VEGFR-2 and VEGFR-3 are expressed on proliferating vascular and lymphatic endothelial cells (see page 15, lines 14-15, page 16, line 4-5, in particular).

The claimed invention as recited in claim 12 differs from the teachings of the reference only in that the method wherein the neoplastic disease is breast ductal carcinoma, squamous cell carcinoma, and prostate cancer.

The claimed invention as recited in claim 22 differs from the teachings of the reference only in that the method further comprises exposing the sample to a second compound that binds to at least one of VEGFR-2 and VEGFR-3.

The claimed invention as recited in claim 27 differs from the teachings of the reference only in that the method further comprises exposing the sample to a second compound that binds to VEGFR-3.

Achen *et al* teach human VEGF-D is a ligand for VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4) and VEGF-D is most closely related to VEGF-C (See Abstract, Fig 1, page 550, column 2, bridging page 551 column 2, in particular). Achen *et al* further teach VEGF-C regulates angiogenesis of the lymphatic vasculature because VEGFR-3 is strongly expressed by the lymphatic endothelium while VEGFR-2 is expressed in vascular endothelial cells (See page 553, column 1, first two full paragraph, in particular). Achen *et al* teach VEGF-D and VEGF-C exists at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular).

Valtola *et al* teach that VEGF-C and VEGFR-3 are associated with angiogenesis in breast cancer (See entire document, in particular). Valtola *et al* teach VEGFR-3 is expressed weakly in the blood vessels of normal breast tissue (see page 1384, column 2, first paragraph, in particular) while intraductal carcinomas is stained positive for VEGFR-3 in invasive breast carcinoma as

detected by antibody that binds specifically to VEGF-C and VEGFR-3 (See Fig 1, page 1384, column 2, VEGFR-3 positive vessels intraductal carcinomas, in particular).

Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, squamous cell carcinoma, and melanoma (See page 105, Table 1, in particular). Salven *et al* further teach some tumor such as ductal breast carcinomas and adenocarcinomas do not express any of the known VEGFs, suggesting in these tumors, other angiogenic stimuli such as VEGF-D may be providing the stimuli in these cases (See page 106, column 2, Note added in proof, in particular).

Tsurusaki *et al* teach lymph node dissemination is a major prognostic factor in human cancer. VEGF-C in prostatic carcinoma is significantly higher in lymph node-positive group than in lymph node-negative group. In addition, the number of VEGFR-3-positive vessels is increased in stroma surrounding VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen for breast ductal carcinoma as taught by Valtola *et al* using the monoclonal antibody that binds specifically to VEGF-D for a method for screening for a neoplastic disease as taught by the WO 99/33485 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Achen *et al* teach VEGF-D and VEGF-C exists al at the functional level because VEGF-D binds to the same receptors as those of VEGF-C (See page 552, Figure 4, in particular). Valtola *et al* teach VEGF-C and VEGFR-3 are associated with angiogenesis in ductal carcinoma (See entire document, in particular). Salven *et al* teach VEGF-C mRNA is detected in human tumor such as breast carcinoma, and squamous cell carcinoma. Tsurusaki *et al* teach the number of VEGFR-3-positive vessels is increased in stroma surrounding the VEGF-C-positive prostatic carcinoma cells, implicating lymph node metastasis (See Abstract, in particular). Claims 22 and 27 are included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to detect VEGFR-2 and VEGFR-3 using antibody that binds to VEGFR-2 and VEGFR-3 because the WO 99/33485 publication teaches VEGF-D binds to both VEGFR-2 and VEGFR-3 (see page 45, pages 13-14, in particular) and antibody to VEGFR-2 and VEGFR-3 may also be used since VEGF-D, VEGFR-2 and VEGFR-3 are

expressed on proliferating vascular and lymphatic endothelial cells (see page 15, lines 14-15, page 16, line 4-5, in particular).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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